Pancreatic Cancer

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MedNet21
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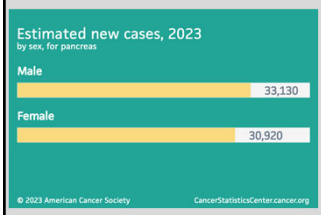
Aims and Objectives

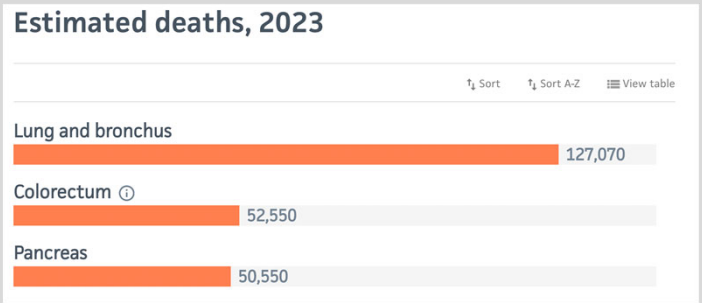
- Discuss the epidemiology and trends of pancreatic cancer in the United States
- Provide an overview of the workup and diagnosis of patients with suspected pancreatic cancer
- Provide an overview of treatment strategies based on the stage of disease

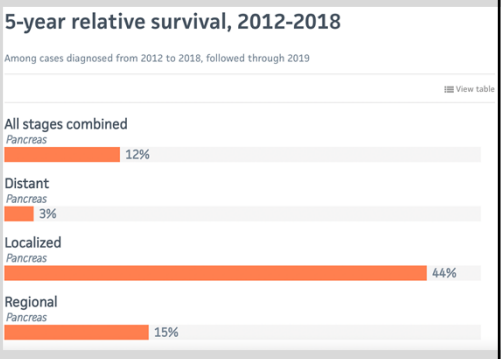
Epidemiology



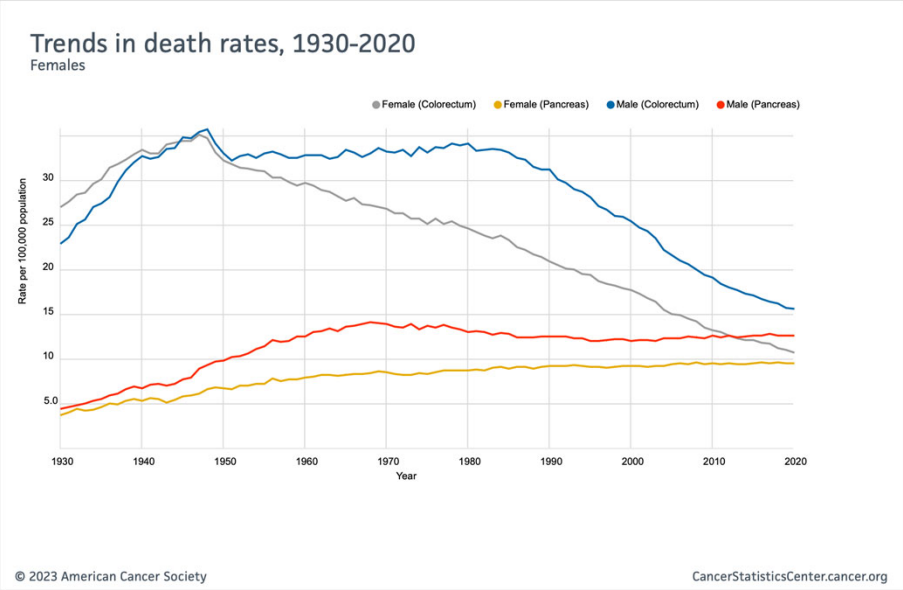
Estimated new cases, 2023	Estimated deaths, 2023	Incidence rates, 2015-2019	Death rates, 2016-2020
64,050	50,550	13.2	11.1
		Average annual rate per 100,000, age adjusted to the 2000 US standard population.	Average annual rate per 100,000, age adjusted to the 2000 US standard population

Survival

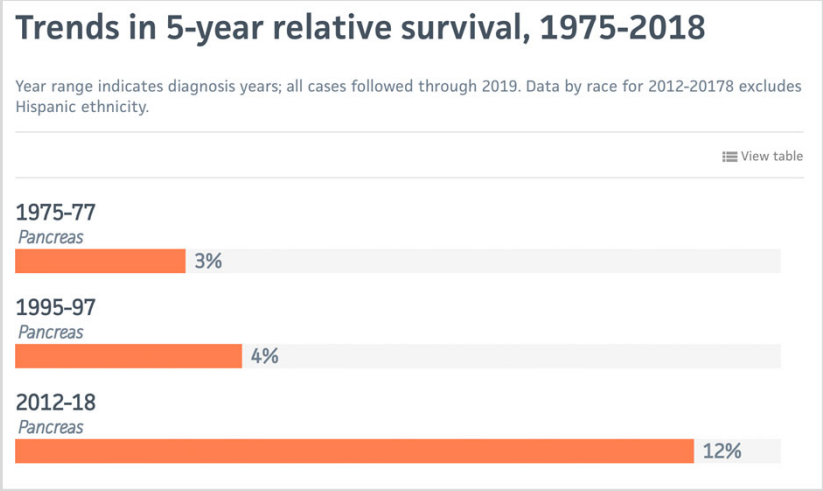




Survival



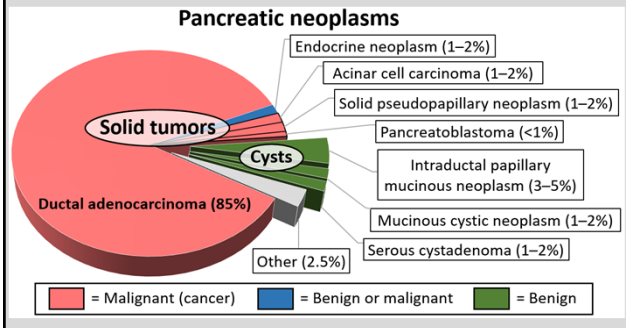
Survival

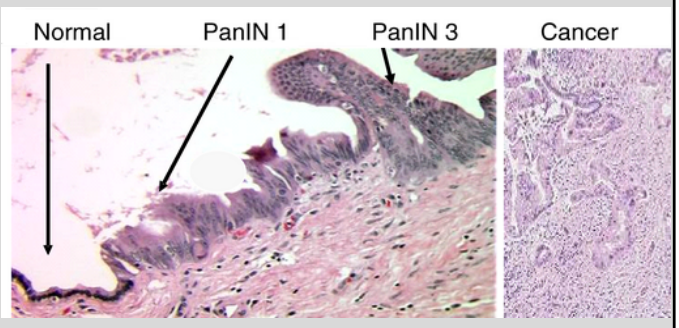


Risk Factors

Hereditary	Hereditary pancreatitis (PRSS1):	**50-80** fold increase
	BRCA:	**3.5-10** fold increase
	FMMS (TP16):	**20-34** fold increase
	Peutz-Jeghers (STK11):	**75-132** fold increase
Environmental	Smoking: **74%** increased risk	
	Environmental carcinogens (asbestos, PAH, DDT, etc.)	
	Obesity	
	Alcohol and coffee are associated with mixed risk	

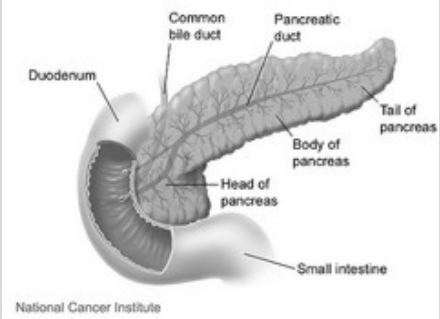
Pre-Malignant Lesions





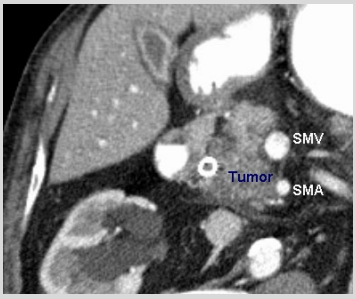
Diagnosis and Workup

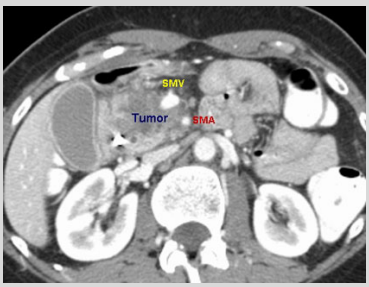
- Laboratory Studies – CBC, CMP/LFTs, CA19-9
- Imaging – Triple phase contrast-enhanced protocol CT with fine cuts
- EUS & ERCP
  - Evaluation and biopsy
  - Biliary stenting if jaundiced



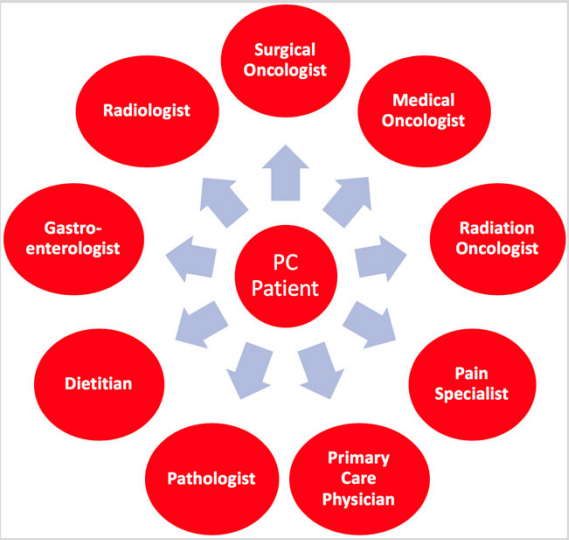
Diagnosis and Workup

- Anatomical Staging
  - Resectable
    - <180 degree involvement of SMV, no involvement of arterial structures
  - Borderline Resectable
    - Re-constructible involvement of SMV, <180 degree involvement of arterial structures
  - Locally Advanced
    - Unreconstructible SMV, >180 degree involvement of arterial structures
  - Metastatic Disease





Multi-Disciplinary Approach to Pancreatic Cancer Care



Active Cancer Treatment

- Chemotherapy
  - Neoadjuvant vs. Adjuvant vs. Palliative
- Surgical Resection
  - Open vs. Minimally-invasive
- Radiation Therapy
  - Preoperative, intraoperative, postoperative

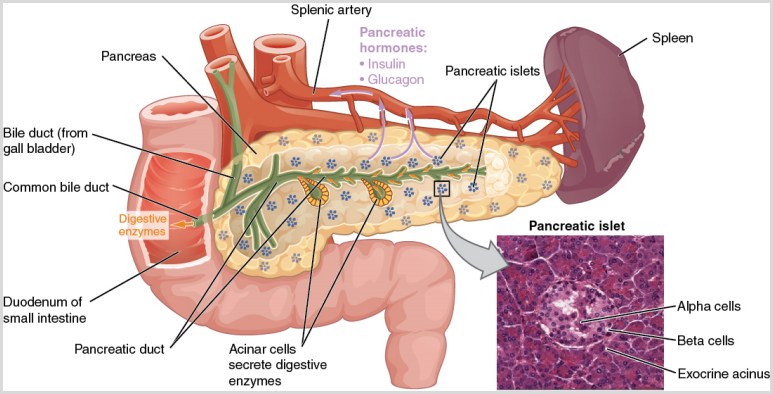
Chemotherapy

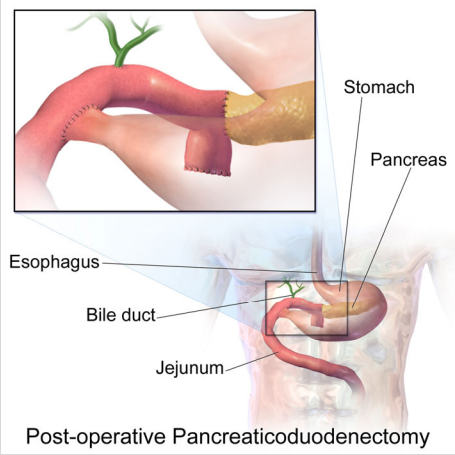
- Regimens
  - FOLFIRINOX – 5-FU, Leucovorin, Irinotecan, Oxaliplatin
  - Gemcitabine/nab-Paclitaxel
  - Gemcitabine/Capecitabine
- Neoadjuvant Chemotherapy - +BR, +LAPC, +/- Resectable
  - Increased proportion of patients who receive chemotherapy
  - Downstage Tumor
  - Selection/Assess Biology of Disease
  - Improve survival?

Neoadjuvant Chemotherapy

- Resectable
  - 6 randomized trials – Heterogeneity with type of regimen used (chemotherapy vs. chemoradiotherapy)
  - Unknown/Potential improvement in disease-free or overall survival
- Borderline Resectable
  - Improved R0 resection rate, potential improved survival
- Locally Advanced
  - Improved resection rate, improved survival for those undergoing surgery

Surgical Resection





Surgical Resection

- Mortality <2%
- Morbidity – ~50%
  - Postoperative pancreatic fistula, delayed gastric emptying, bleeding
- Length of Stay ~ 7days

- Minimally-Invasive Surgery
  - Smaller incisions, potentially less pain
  - Potentially faster recovery and reduced length of stay
  - Higher costs, learning curve

Surgical Resection

- Volume improves outcome for patients undergoing pancreatectomy
  - Any complication HR 0.73
  - 90-day mortality HR 0.65
  - Improved cancer-specific outcomes including lymph node yield, R0 resection rates

Adjuvant Chemotherapy

- ESPAC-4
  - 732 patients randomized to gemcitabine/capecitabine vs. gemcitabine
  - Median OS 28 vs. 25.5 months
  - 5-year survival 29% vs. 16%
- PRODIGE-24
  - 493 patients randomized to FOLFIRINOX vs. gemcitabine
  - Median OS 54.4 vs. 35 months

Radiotherapy

Adjuvant	Neoadjuvant
• Meta-analysis of 4 RCT showed no benefit in OS (R1 benefit?)	• PREOPANC – Resectable and BR randomized to CRT vs. upfront surgery + chemotherapy • Improved OS (HR 0.73), median OS 15.7 vs. 14.3 months, 5-year OS 20.5% vs. 6.5%

19

Future Directions

- Early detection, improved biomarkers
- Improved local therapies – radiation therapy, irreversible electroporation, ablative therapies, aggressive surgical resection
- Immunotherapy, vaccines, targeted therapies (KRAS etc.)

Conclusions

- Premalignant lesions are common and should be evaluated/managed by multidisciplinary teams
- Newer and improved systemic and surgical therapy have resulted in a higher proportion of patients eligible for surgery and improved survival
- Multi-disciplinary evaluation and care by high volume providers optimize outcomes

Pancreatic Cancer

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Hereditary pancreatic cancer

- 10-15% of pancreatic cancer is genetic
- Up to 10% of patients with pancreatic cancer have a family history of pancreatic cancer

Genetic screening

- **Referral to genetics (ASCO clinical opinion)**
  - All patients with pancreatic cancer
  - Genetic syndromes associated with pancreatic cancer. Lynch, Peutz-Jeghers, Li-Fraumeni, BRCA
  - 2 first-degree relatives with pancreatic cancer
  - 3 or more relatives on same side of family with pancreatic cancer
  - Hereditary pancreatitis

Screening for pancreatic cancer

- Still a field in development with data emerging
- Candidates for screening – Individuals at high risk
  - Known genetic syndromes
  - Strong family history
- Age to begin screening determined by relative risk. E.g. Peutz-Jegher syndrome starts at a younger age

Screening for pancreatic cancer

- Screening modalities
  - EUS
  - MRCP
- If normal, imaging is usually repeated annually
  - Often alternating EUS and MRCP
- Goal is to identify early invasive cancers, and precancerous lesions

Presenting signs and symptoms

- Depends on tumor location
- Head : 60-70 % of cancers
- Body/Tail : 20-25% of cancers

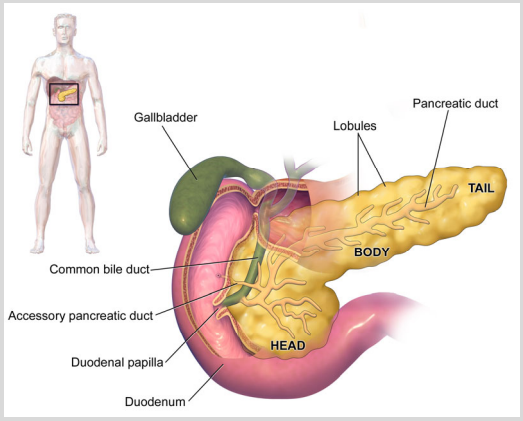


Image : Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014
Ann Oncol. 1999;10 Suppl 4:82

Presenting signs and symptoms

- Head :
  - Jaundice
  - Steatorrhea
  - Weight loss
- Jaundice – early sign in pancreatic head tumors
  - Pts presenting with painless jaundice may have better prognosis than those with pain

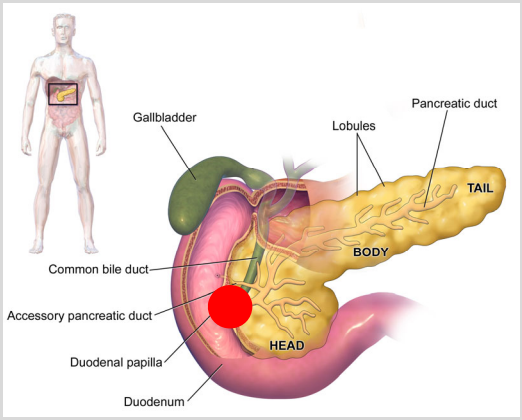


Image : Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014

Presenting signs and symptoms

- Any location
  - Asthenia
  - Anorexia/weight loss
  - Pain
  - Nausea/vomiting
  - Unexplained thromboembolic events

  (hypercoagulable state)

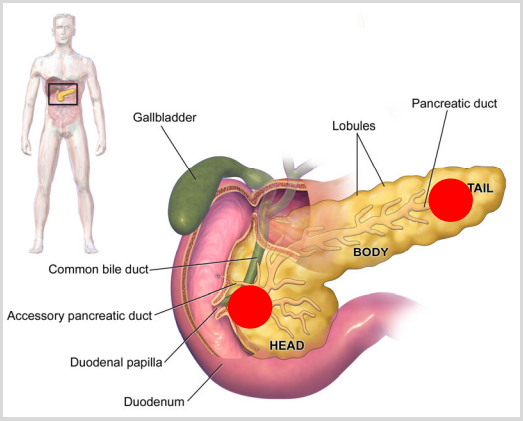


Image : Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014

Presenting signs and symptoms

Pain

- Very common symptom, even with small tumors
- Insidious in onset
- Often epigastric
- Gnawing visceral quality
  - Radiates to sides/back
- Often worse at night
- Severe back pain – Body/tail tumor

Presenting signs and symptoms

New onset diabetes

- In upto 25% of pancreatic cancer
- Pooled analysis of a total of 88 studies (50 cohort and 39 case-control studies)
  - Overall relative risk of pancreatic cancer in diabetics vs. non-diabetics was 1.97 (95 % CI 1.78-2.18)
  - Risk of pancreatic cancer greatest early after diagnosis of diabetes, but remained elevated
- Unclear whether pancreatic cancer is a CAUSE or CONSEQUENCE of diabetes

Clin Gastroenterol Hepatol. 2004;2(6):510.
Gastroenterology. 2005;129(2):504.
Ann Surg Oncol. 2014 Jul;21(7):2453-62.

Presenting signs and symptoms

Patients with metastatic (Stage IV cancer)

- Any of the previously mentioned signs/symptoms
- Abdominal mass
- Ascites
- Palpable periumbilical mass (Sister Mary Joseph's node)

Diagnosis

- Cannot be diagnosed by signs/symptoms alone
  - Study of 70 patients with highly suggestive signs/symptoms
  - Patients underwent diagnostic surgery
  - Only 30 had pancreatic cancer

N Engl J Med. 1977;297(14):737.

Diagnosis

- Jaundice and/or epigastric pain
  - LFTs including bilirubin
  - Lipase for acute pancreatitis
  - CA 19-9 (tumor marker) can be useful
    - Low sensitivity when jaundiced (elevated in biliary obstruction)
    - More sensitive with larger tumors
    - Needs Lewis blood group to be expressed (Absent in 5-10% of population)
- Imaging for Jaundice
  - US – high sensitivity for biliary obstruction. Can detect pancreatic masses
  - CT A/P – Can also identify metastatic disease

Diagnosis – After initial imaging is positive

- Imaging
  - CT Abdomen/Pelvis ("pancreatic protocol" – multiphase contrast)
  - CT Chest with contrast – To identify thoracic metastases
  - MRI may be used instead of CT Abdomen/Pelvis
- ERCP
  - If biliary decompression/stent placement required
  - Cytology sampling can also be performed
  - Make sure CT (or MRI) is done BEFORE stent placement. Can alter imaging findings, obscure tumor

Diagnosis – After initial imaging is positive

- Endoscopic ultrasound (EUS)
  - Allows for biopsy
- Biopsy is not always required for patients with localized mass that is resectable and has typical imaging findings.
  - Can be taken straight to surgery

Diagnosis – After initial imaging is positive

Metastatic disease

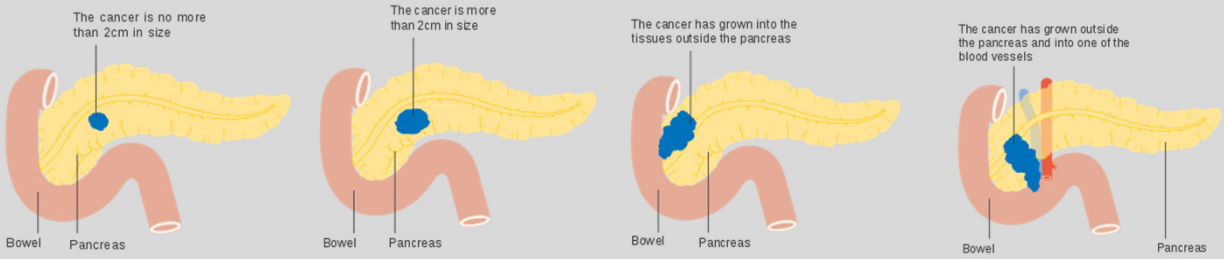
- **Get Biopsy**
  - For diagnosis and molecular testing (to plan treatment)
  - Preferably from metastatic site, e.g. liver

    Can be done percutaneously with more tissue collected (core biopsy)
  - Percutaneous biopsy of pancreatic tumor generally avoided, due to theoretical risk of tumor tracking
  - EUS guided FNA of pancreatic tumor yields limited tissue, usually only cytology.
    Cannot be used for molecular testing

Referrals

- Medical oncology
- Surgical oncology

Treatment – localized cancer



T1 T2/T3 Borderline resectable Unresectable

Resectable

Images: Cancer Research UK / Wikimedia Commons

Treatment – localized cancer

- Goals of therapy
  - Cure
- Five year survival by stage
  - Stage IA – 39 percent
  - Stage IB – 34 percent
  - Stage IIA – 28 percent
  - Stage IIB – 21 percent
  - Stage III – 11 percent
- **High rates of recurrence, even for early-stage tumors**

JAMA Surg. 2018;153(12):e183617.

Treatment – Advanced/Metastatic cancer

- Includes those with unresectable tumors, or recurrence after surgery
- Goals of therapy
  - Prolong survival
  - Improve symptoms and quality of life
- Treatment options
  - Chemotherapy
  - Immunotherapy
  - Targeted therapy
  - **Clinical trials**
- Average survival
  - ~ 1 year

Supportive care

- **Pain**
- Common in advanced cancer – usually epigastric
- Opioids are mainstay of therapy – need to be titrated based on response
- Transdermal patch (like fentanyl) useful in patients with nausea/vomiting
- Consider treating neuropathic component (due to proximity to celiac plexus). Eg. Gabapentin, pregabalin, duloxetine
- Nerve block if not controlled with opioids
  - Celiac plexus or splanchnic nerves

Supportive care

- **Venous thromboembolism (VTE)**
- Advanced pancreatic cancer causes hypercoagulable state
- Routine prophylaxis for ambulatory patients not usually recommended
  - Can be considered for high-risk patients (high Khorana score, prior history of unprovoked VTE)
- **All patient should be counselled on warning symptoms. Low threshold for testing (i.e. CT angio)**

Supportive care

- **Venous thromboembolism (VTE)**
- If VTE is diagnosed and patient has active cancer
  - Indefinite anticoagulation unless contraindicated (very high risk of recurrent VTE)
  - LMW heparin, DOAC
  - Warfarin is acceptable alternative

Supportive care

- **Infection**
- Biliary stents
  - Risk of acute cholangitis due to introduction of intestinal flora into biliary system
  - Important to recognize in patients with biliary stent
  - Requires urgent hospitalization and IV antibiotics
- **Stent occlusion**
  - Suspect if worsening jaundice, rising bilirubin
  - Need repeat ERCP/ stent replacement

Supportive care

- **Anorexia/weight loss**
  - Dietician consultation
  - Small frequent meals
  - May use appetite stimulants

Supportive care

- **Pancreatic insufficiency**
  - Steatorrhea (loose, greasy, foul-smelling stools)
  - Flatulence
  - Weight loss
- Due to obstruction of pancreatic duct, or loss of pancreatic tissue – lack of pancreatic enzyme
  - Obstruction of pancreatic duct by tumor
  - Due to surgery or radiation
- Treat with pancreatic enzymes – with meals AND snacks
  - Titrate dose as needed

Supportive care

- **Depression/Anxiety**
- Common due to new diagnosis, often incurable disease
- Can be a presenting symptom (prodrome) of pancreatic cancer, often in the elderly
- Discuss psychosocial concerns, support systems
- May need antidepressants/antianxiety medication

Supportive care

- **Management of chronic issues**
- Dose of antihypertensives and antidiabetics may need to be reduced due to weight loss
  - Risk of hypoglycemia (insulin, sulfonylureas) due to anorexia and weight loss
- In advanced/metastatic pancreatic cancer with limited life expectancy
  - Try to minimize medication burden (e.g., statins)
  - Less restrictive BP and glucose/A1C goals
  - Routine cancer screening may not be necessary (e.g., mammogram, colonoscopy)

Conclusion

- Identification and screening for high-risk patients is an area of active research
  - Consider referring patients with risk factors (such as family history) to Cancer Genetics to estimate risk and discuss pros/cons of genetic testing and screening
- Characteristic signs/symptoms - raises suspicion for further workup
- Management of pancreatic cancer is multi-faceted
  - Managing comorbidities and supportive care in parallel with cancer-directed therapies